

[Chem. Pharm. Bull.]
28(11)3172-3177(1980)

Cyclic Guanidines. XIII.¹⁾ Synthesis of 2-Amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine Derivatives²⁾

FUMIYOSHI ISHIKAWA and HITOSHI YAMAGUCHI

Research Institute, Daiichi Seiyaku Co., Ltd.³⁾

(Received March 22, 1980)

A method for the synthesis of 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives (**12** and **13b**) is described. Reduction of the 3-substituted 2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (**4c**) and -2-thione (**9b**, **c**) with sodium borohydride gave the 1,2,3,4-tetrahydro derivatives (**6c** and **10b**, **c**), whereas the 3-unsubstituted compound **4a** could be reduced only with lithium aluminum hydride to afford the 1,2,3,4-tetrahydro derivative **6a**. The 2-chloro derivative (**7**) was reduced with sodium borohydride to give the 2-chloro-3,4-dihydro derivative **8a**, which was reacted with ethyl bromoacetate to yield predominantly the 3-substituted derivative (**8c**). Amination of **8c** gave compound **12**. Methylation of **10b** and **10c**, followed by amination similarly yielded **13b** and **12**, respectively. In this amination some oxidative products (**14**) were also obtained. Compounds **12** and **13b** had lower inhibitory effects against blood platelet aggregation than the quinazoline analogs (**1**) and (**2**).

Keywords—partial reduction of thieno[2,3-*d*]pyrimidine; 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine; 5-phenyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]thieno[2,3-*d*]pyrimidin-2-one; oxidative rearrangement; blood platelet aggregation inhibitor

We have found that 2-amino-3-benzyl-4-phenyl-3,4-dihydroquinazoline (**1**) shows blood platelet aggregation inhibitory action.⁴⁾ It was also reported that 6-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one (**2**) is a potent inhibitor.⁵⁾ This paper deals with the synthesis of the thieno analogs of **1** and **2**, *i.e.*, 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives (**13b** and **12**).

Although the 2-amino-3-aminomethylthiophene derivative may be a suitable intermediate for the preparation of 3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives, its preparation is difficult because of the instability of 2-aminothiophene derivatives.⁶⁾ Only 4-alkyl-3,4-dihydrothieno[2,3-*d*]pyrimidines were obtained by the reaction of thieno[2,3-*d*]pyrimidine with alkyl lithiums.⁷⁾ However, we were able to reduce various 4-phenylthieno[2,3-*d*]pyrimidines selectively to obtain the dihydro derivatives.

2-Amino-3-benzoyl-4,5-dimethylthiophene⁸⁾ (**3**) was heated with urea at 200° to give the corresponding 2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (**4a**). Reaction of **3** with ethyl isocyanatoacetate in toluene under reflux gave the 3-substituted compound **4c**, whereas at room temperature the product was a noncyclized intermediate (**5c**) which was converted into **4c** on

- 1) Part XII: F. Ishikawa, *Chem. Pharm. Bull.*, **28**, 2587 (1980).
- 2) This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, April 1980.
- 3) Location: 1-16-13 Kitakasai, Edogawa-ku, Tokyo 132, Japan.
- 4) F. Ishikawa, Y. Watanabe, and J. Saegusa, *Chem. Pharm. Bull.*, **28**, 1357 (1980).
- 5) W.N. Bevering and R.A. Partyka, *J. Med. Chem.*, **18**, 225 (1975).
- 6) H.D. Hartough, "The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, 1952, p. 228; D.L. Eck and G.W. Stacy, *J. Heterocycl. Chem.*, **6**, 147 (1969); S. Blechert, R. Gericke, and E. Winterfeldt, *Chem. Ber.*, **106**, 368 (1973); K. Gewald, *Khim. Geterotsikl., Soedin.*, **1976**, 1299.
- 7) J. Bourguignon, M. Moreau, G. Queguiner, and P. Pastour, *Bull. Soc. Chim. Fr.*, **1977**, 676.
- 8) N. Nakanishi, T. Tahara, K. Arai, M. Shiroki, T. Tsumagari, and Y. Takigawa, *J. Med. Chem.*, **16**, 214 (1973).

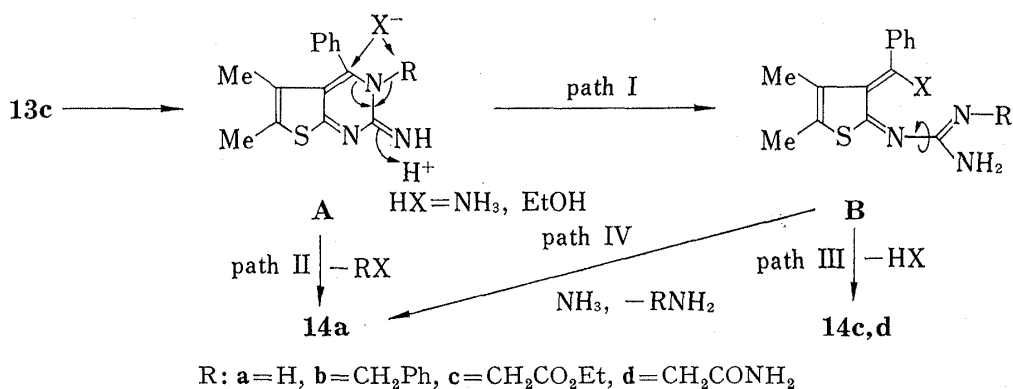
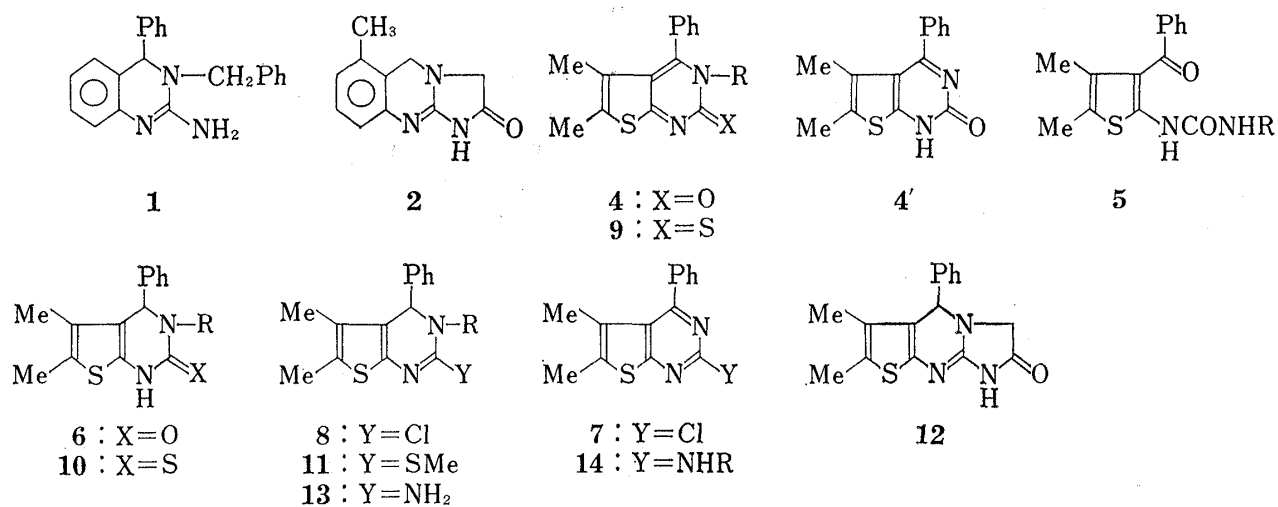


Chart 1

heating. The structure of **5c** was confirmed by nuclear magnetic resonance (NMR) spectroscopy: the proton on the nitrogen adjacent to the methylene group was observed at δ 6.24 as a triplet coupled with the methylene protons.

According to the reported procedure for the reduction of 3-substituted 2,3-dihydroquinazolin-2-ones,⁹⁾ **4c** was treated with sodium borohydride to give the 3,4-dihydro-2(1H)-one derivative (**6c**). Compound **4a** was not reduced by this reagent, but reduction with lithium aluminum hydride gave the corresponding compound (**6a**). Compound **4a** may exist as the tautomeric structure **4'a**, while **4c** takes a fixed *ortho* quinoid form. The reduction of **4c**, therefore, proceeded easily.

An attempt to chlorinate **6c** with phosphoryl chloride to provide the 2-chloro-3-ethoxycarbonylmethyl derivative (**8c**) was unsuccessful, whereas treatment of **4a** with phosphoryl chloride gave the 2-chloro derivative (**7**). By adaptation of the method used for the reduction of 2-chloro-4-phenylquinazoline,¹⁰⁾ **7** was treated with sodium borohydride to give the corresponding 2-chloro-3,4-dihydrothieno[2,3-*d*]pyrimidine derivative (**8a**). Heating **8a** with ethyl bromoacetate in the presence of finely powdered potassium carbonate in methyl ethyl ketone gave predominantly the 3-substituted product (**8c**), as in the alkylation of 3,4-dihydroquinazoline.¹¹⁾ Reaction of **8c** with ammonia in a sealed tube under a nitrogen atmosphere

9) W. Metlesics, G. Silverman, V. Toome, and L.H. Sternbach, *J. Org. Chem.*, **31**, 1007 (1966).

10) G.N. Walker, S. Afr. Patent 6705040 (1968) [*Chem. Abstr.*, **70**, 106556 (1969)].

11) W.L.F. Armarego, "The Chemistry of Heterocyclic Compounds: Fused Pyrimidine Part I. Quinazolines," Interscience Publishers, Inc., New York, 1967, p. 403.

yielded the desired compound **12**, which was identical with a sample prepared by the reaction of **11c** with ammonia as described below.

Heating **3** with isothiocyanates gave 3-substituted 2,3-dihydrothieno[2,3-*d*]pyrimidine-2-thiones (**9b, c**), which were easily reduced by treatment with sodium borohydride to 3,4-dihydro-2(1H)-thiones (**10b, c**). Methylation of **10b, c** with methyl iodide, followed by reaction with ammonia under a nitrogen atmosphere also gave the desired compounds **13b** and **12**, respectively. The reaction of **11c** with ammonia in the presence of air afforded compounds **12, 14a, 14c** and **14d** in 37, 9, 1 and 16% yields, respectively. In the NMR spectra of **14c, d**, the methylene protons of the carbonylmethylamino group were observed as a doublet. UV spectra of **14** were similar to those of **4** rather than to those of the 3,4-dihydro derivatives (**6**) or (**13**). Compounds **14a, d** were identical with the samples prepared by the reaction of **8a** with ammonia and glycnamide, respectively.

The formation of **14a, c, d** from **13c** can be explained by in terms of the routes shown in Chart 1. 2-Amino-3,4-dihydrothieno[2,3-*d*]pyrimidine (**13c**) is unstable under oxidative conditions in favor of the dehydro imino derivative (**A**), which yields **14c, d** through Path I and Path III by a reaction similar to Dimroth's rearrangement in the case of 3-alkyl-2-iminoquinazoline.¹²⁾ Compound **14a** is formed through Path II or Paths I and IV. This mechanism is supported by the fact that **13b** itself is stable but is readily oxidized with chloranil to give the rearrangement product (**14b**).

The blood platelet aggregation inhibitory activities of the 2-amino-3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives (**12** and **13b**) are less potent than those of the corresponding benzene analogs, **1** and **2**, respectively.

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. UV spectra were taken with a Hitachi 124 spectrometer. Mass spectra (MS) were determined on a JEOL OISG-2 mass spectrometer. NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Hitachi R-40 (90 MHz) spectrometer with tetramethylsilane as an internal standard. The abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. For column chromatography on silica gel and preparative thin-layer chromatography, we used Merck Kieselgel (70–230 mesh) and Merck Kieselgel 60 GF₂₅₄, respectively.

5,6-Dimethyl-4-phenyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (4a)—A mixture of 3.46 g (15 mmol) of **3** and 1.0 g (18 mmol) of urea was heated at 170–200° for 2 hr. The reaction mixture was cooled, then a small amount of MeOH was added to give 1.44 g of an insoluble material, which was filtered off. The MeOH solution was concentrated *in vacuo* and benzene was added to the residue to give 1.56 g of insoluble material. The insoluble materials were combined and recrystallized from AcOH–AcOEt to give 1.90 g (50%) of **4a**, mp 253–259°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3240–3100, 1620. NMR (CDCl₃) δ : 1.57 (3H, s, 5-CH₃), 2.24 (3H, s, 6-CH₃), 7.41 (5H, s, Ph). *Anal.* Calcd for C₁₄H₁₂N₂O₂S: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.50; H, 4.82; N, 10.93.

Ethyl 5,6-Dimethyl-4-phenyl-2-oxo-2,3-dihydrothieno[2,3-*d*]pyrimidine-3-acetate (4c)—A mixture of 3.48 g (15 mmol) of **3**, 3 drops of Et₃N and 7.00 g of ethyl isocyanatoacetate¹³⁾ in 40 ml of dry toluene was stirred at room temperature for 20 hr and heated under reflux for 4 hr. Insoluble material was filtered off and the filtrate was diluted with benzene. The solution was washed with H₂O, dried, and concentrated. The residue was recrystallized from benzene–petr. ether to give 3.42 g (67%) of **4c**, mp 173–177°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1750, 1655. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 231, 256, 282, 293 (s), 377. NMR (CDCl₃) δ : 1.16 (3H, t, CH₃), 1.25 (3H, s, 5-CH₃), 2.22 (3H, s, 6-CH₃), 4.13 (2H, q, CH₂), 7.2–7.65 (5H, m, Ph). *Anal.* Calcd for C₁₈H₁₈N₂O₃S: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.78; H, 5.28; N, 8.18.

Ethyl [3-[2-(3-Benzoyl-4,5-dimethyl)thienyl]ureido]acetate (5c)—By a procedure similar to that described above, 1.16 g (5 mmol) of **3** was treated with ethyl isocyanatoacetate at room temperature to give 0.22 g (11%) of **5c**, mp 144–146° (from CHCl₃–petr. ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300, 1640, 1595, 1540, 1505, UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 253, 268 (s), 373. NMR (CDCl₃) δ : 1.20 (3H, t, CH₃), 1.50 (3H, s, 4-CH₃), 2.65 (3H, s, 5-CH₃), 3.85 (2H, d, N-CH₂), 4.15 (2H, q, O-CH₂), 6.24 (1H, br t, N-H), 7.44 (5H, s, Ph), 10.92 (1H, br s, N-H). *Anal.* Calcd for C₁₈H₂₀N₂O₄S: C, 59.98; H, 5.59; N, 7.77. Found: C, 59.98; H, 5.60; N, 7.63.

12) D.J. Brown and B.T. England, *Australian J. Chem.*, **21**, 2813 (1968).

13) W. Siefken, *Ann.*, **562**, 75 (1945).

5,6-Dimethyl-4-phenyl-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-2-one (6a)—Compound **4a** (1.28 g, 5 mmol) was added portionwise to a suspension of 0.57 g (15 mmol) of LiAlH_4 in 50 ml of THF at 15–25° during 0.5 hr with stirring. The mixture was heated at 50–55° for 2 hr then under reflux for 1 hr. It was cooled, then 1 ml of H_2O was added dropwise below 20°. The mixture was concentrated *in vacuo* and 20 ml of 10% HCl was added to the residue. The precipitate was collected, washed with 10% HCl, and recrystallized from DMF to give 0.75 g (58%) of **6a**, mp 279–283° (dec.). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3180, 3060, 2900, 1680. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 235 (s), 283. NMR ($\text{DMSO}-d_6$) δ : 1.63 (3H, s, 5- CH_3), 2.11 (3H, s, 6- CH_3), 5.30 (1H, d, $J=3$ Hz, CH), 7.28 (5H, s, Ph), 9.40 (1H, br, N-H). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{OS}$: C, 65.09; H, 5.35; N, 10.36. Found: C, 64.62; H, 5.46; N, 10.84.

Ethyl 5,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-3-acetate (6c)— NaBH_4 (0.38 g, 10 mmol) was added to a solution of 3.40 g (10 mmol) of **4c** in 20 ml of CHCl_3 -EtOH (1:1). The mixture was stirred at room temperature for 0.5 hr and concentrated *in vacuo*. After addition of H_2O to the residue, the mixture was neutralized with 1 N HCl and extracted with CHCl_3 . The extract was washed with H_2O , dried, and concentrated *in vacuo*. The residue was recrystallized from CHCl_3 -EtOH to give 2.89 g (85%) of **6c**, mp 208–211°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3290, 3170, 2900, 1740, 1650, 1610. NMR (CDCl_3) δ : 1.22 (3H, t, CH_3), 1.61 (3H, s, 5- CH_3), 2.13 (3H, s, 6- CH_3), 3.47, 4.52 (1H \times 2, d \times d, $J=18$ Hz, N- CH_2), 4.16 (2H, q, CH_2), 5.39 (1H, s, CH), 7.30 (5H, s, Ph), 8.78 (1H, br s, N-H). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.72; H, 5.86; N, 8.19.

Corresponding 2-thione derivatives **10b**, **c** were similarly prepared.

10b: Yield 100%, mp 205–206° (from CHCl_3 -hexane). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3150, 2970, 1610, 1520, 1480, 1280. NMR (CDCl_3) δ : 1.61 (3H, s, 5- CH_3), 2.13 (3H, s, 6- CH_3), 3.98, 6.43 (1H \times 2, d \times d, $J=15$ Hz, N- CH_2), 5.35 (1H, s, CH), 7.3–7.5 (10H, m, Ph), 10.65 (1H, br, N-H). Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{S}_2$: C, 69.19; H, 5.53; N, 7.68. Found: C, 69.39; H, 5.57; N, 7.74.

10c: Yield 75%, mp 251–254° (from CHCl_3 -petr. ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3150, 2980, 1740, 1200. NMR (CDCl_3) δ : 1.27 (3H, t, CH_3), 1.67 (3H, s, 5- CH_3), 2.18 (3H, s, 6- CH_3), 3.85, 5.30 (1H \times 2, d \times d, N- CH_2), 4.22 (2H, q, CH_2), 5.54 (1H, s, CH), 7.33 (5H, s, Ph), 9.35 (1H, br s, N-H). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2$: C, 59.97; H, 5.59; N, 7.77. Found: C, 59.99; H, 5.69; N, 7.76.

2-Chloro-5,6-dimethyl-4-phenylthieno[2,3-d]pyrimidine (7)—DMF (6.2 ml, 80 mmol) was added dropwise to 15 ml of POCl_3 below 30° with stirring. After addition of 5.16 g (20 mmol) of **4a** to the mixture, it was heated at 75–90° for 3 hr with stirring, poured into ice-water and extracted with CHCl_3 . The extract was washed with H_2O , dried, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with benzene to give 3.79 g (69%) of **7**, mp 126–128° (from benzene-petr. ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1480, 1210. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 249, 295, 322 (s). NMR (CDCl_3) δ : 1.82 (3H, s, 5- CH_3), 2.47 (3H, s, 6- CH_3), 7.40 (5H, s, Ph). Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{S}$: C, 61.20; H, 4.04; N, 10.20. Found: C, 61.15; H, 3.99; N, 10.19.

2-Chloro-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine (8a)—By a procedure similar to that described for the preparation of **6c**, 3.05 g (11 mmol) of **7** was treated with 2.09 g (55 mmol) of NaBH_4 in CHCl_3 -EtOH to give 1.75 g (63%) of **8a**, mp 215–218° (from CHCl_3 -hexane). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3180, 1590, 1280. NMR (CDCl_3) δ : 1.60 (3H, s, 5- CH_3), 2.21 (3H, s, 6- CH_3), 5.30 (1H, br, N-H), 5.71 (1H, d, CH), 7.30–7.45 (5H, m, Ph). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{S}$: C, 60.75; H, 4.73; N, 10.12. Found: C, 60.75; H, 4.69; N, 10.19.

Ethyl 2-Chloro-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine-3-acetate (8c)—A mixture of 0.83 g (3 mmol) of **8a**, 0.55 g (3.3 mmol) of ethyl bromoacetate and 0.83 g (6 mmol) of finely powdered K_2CO_3 in 50 ml of MeCOEt was heated under reflux for 4 hr with stirring under a nitrogen atmosphere. Insoluble material was filtered off and washed with MeCOEt. The combined filtrate and washings were concentrated. The oily residue was crystallized from EtOH to give 0.475 g (44%) of **8c**, mp 119–120° (from CHCl_3 -EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1760, 1560, 1190, 1170. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 230 (s), 248 (s), 265 (s), 333, 346 (s). NMR (CDCl_3) δ : 1.23 (3H, t, CH_3), 1.60 (3H, s, 5- CH_3), 2.22 (3H, s, 6- CH_3), 3.92, 4.27 (1H \times 2, d \times d, $J=18$ Hz, N- CH_2), 4.17 (2H, q, CH_2), 5.64 (1H, s, CH), 7.40 (5H, s, Ph). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{ClN}_2\text{O}_2\text{S}$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.52; H, 5.32; N, 7.91.

3-Benzyl-5,6-dimethyl-4-phenyl-2,3-dihydrothieno[2,3-d]pyrimidine-2-thione (9b)—A mixture of 11.6 g (50 mmol) of **3** and 8.20 g (55 mmol) of benzyl isothiocyanate in 200 ml of EtOH was heated under reflux for 16 hr. The precipitate was collected and washed with cold EtOH to give 7.15 g of **9b**. The filtrate and the washings were combined and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. Elution with benzene- CHCl_3 (7:1) resulted in the recovery of 3.30 g (28%) of **3**, then eluate with CHCl_3 gave 1.37 g of **9b**. Total yield of **9b**, mp 206–207° (from benzene-petr. ether), was 8.88 g (49%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1560, 1380. NMR (CDCl_3) δ : 1.25 (3H, s, 5- CH_3), 2.32 (3H, s, 6- CH_3), 6.04 (2H, br s, N-H), 6.75–7.60 (10H, m, Ph). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{S}_2$: C, 69.58; H, 5.00; N, 7.73. Found: C, 69.37; H, 5.16; N, 7.69.

Ethyl 5,6-Dimethyl-4-phenyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidine-3-acetate (9c)—A mixture of 1.16 g (10 mmol) of **3** and 0.73 g (10 mmol) of ethyl isothiocyanatoacetate¹⁴ in 16 ml of benzene was heated

14) K. Lempert and G. Doleschall, *Acta Chim. Acad. Sci. Hung.*, 37, 457 (1963).

under reflux for 20 hr under a nitrogen atmosphere. After removal of the benzene, the residue was chromatographed on a column of silica gel. The eluate with CHCl_3 gave 0.914 g (51%) of **9c**, mp 201–204° (from CHCl_3 -petr. ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1735, 1230. NMR (CDCl_3) δ : 1.21 (3H, t, CH_3), 1.30 (3H, s, 5- CH_2), 2.31 (3H, s, 6- CH_3), 4.21 (2H, q, CH_2), 5.13 (2H, br s, N- CH_2), 7.3–7.7 (5H, m, Ph). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2\text{S}_2$: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.65; H, 5.18; N, 7.88.

3-Benzyl-5,6-dimethyl-2-methylthio-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine Hydroiodide (11b)—A suspension of 3.65 g (10 mmol) of **9b** and 1.70 g (12 mmol) of CH_3I in 60 ml of EtOH was heated under reflux for 3 hr. After concentration of the mixture to about 10 ml, Et_2O was added to the residue. The precipitate was collected, washed with EtOH- Et_2O (1:1) and dried to give 3.99 g (79%) of **11b**, mp 166–168° (from EtOH- Et_2O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3030, 2890, 1600, 1530, 1500. NMR (CDCl_3) δ : 1.61 (3H, s, 5- CH_3), 2.21 (3H, s, 6- CH_3), 3.34 (3H, s, S- CH_3), 4.43, 5.24 (1H \times 2, d \times d, $J=16$ Hz, N- CH_2), 5.56 (1H, s, CH), 7.2–7.65 (10H, m, Ph). Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{IN}_2\text{S}_2$: C, 52.17; H, 4.58; N, 5.53. Found: C, 52.26; H, 4.72; N, 5.47. The free base of **11b**: mp 155–157° (from benzene-petr. ether).

Compound **11c** was similarly prepared. Yield was 83%, mp 235–243° (from EtOH- Et_2O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3200–2600, 1750, 1540. NMR (CDCl_3) δ : 1.14 (3H, t, CH_3), 1.66 (3H, s, 5- CH_3), 2.19 (3H, s, 6- CH_3), 3.19 (3H, s, S- CH_3), 4.03 (2H, q, CH_2), 4.52 (1H, br s, N-H), 6.01 (1H, s, CH), 7.40 (5H, s, Ph). Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{IN}_2\text{O}_2\text{S}_2$: C, 45.42; H, 4.61; N, 5.58. Found: C, 45.88; H, 4.63; N, 5.79. The free base of **11c**: mp 114–116° (from benzene-petr. ether).

6,7-Dimethyl-5-phenyl-1,2,3,5-tetrahydroimidazo[1,2-a]thieno[2,3-d]pyrimidin-2-one (12)—a) A mixture of 0.37 g (1 mmol) of **8c** in 5 ml of 5% NH_3 -EtOH solution was heated at 120° for 16 hr in a sealed tube under a nitrogen atmosphere. The mixture was cooled, then the precipitate was collected and washed with EtOH and H_2O successively to give 0.042 g (14%) of **12**, mp 287–290° (from CHCl_3 -EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3100–2300, 1730, 1460. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 230 (s), 249, 319. NMR ($\text{CF}_3\text{CO}_2\text{H}$) δ : 1.68 (3H, s, 6- CH_3), 2.31 (3H, s, 7- CH_3), 3.97, 4.48 (1H \times 2, d \times d, $J=20$ Hz, CH_2), 5.90 (1H, s, CH), 7.2–7.6 (5H, m, Ph). MS m/e : 297 (M^+), 220 ($\text{M}-\text{C}_6\text{H}_5$). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{OS}$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.93; H, 5.04; N, 14.32.

b) A mixture of 2.00 g (4 mmol) of **11c** and 1 ml of AcOH in 45 ml of 10% NH_3 -EtOH solution was heated at 100–110° for 60 hr in a sealed tube. The mixture was cooled, then the precipitate was collected by filtration and washed with EtOH to give 0.21 g of **12**. The combined filtrate and washings were concentrated *in vacuo*. Addition of EtOH to the residue gave a further 0.19 g of **12**. The EtOH-soluble fraction was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with CHCl_3 . The extract was washed with H_2O , dried and concentrated *in vacuo*. The residue was chromatographed on silica gel. The first eluate with benzene- CHCl_3 (2:1) gave 0.30 g of the free base of **11c**. The second eluate with benzene- CHCl_3 (2:1) gave 0.18 g of a mixture of **14a** and **14c**, which was separated by preparative thin-layer chromatography with benzene-acetone (10:1) to give 87 mg (9%) of **14a** and 16 mg (1%) of **14c**. Compound **14c**: mp 163–165°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250, 1745, 1550. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 229 (s), 258, 276 (s), 286 (s), 346. NMR (CDCl_3) δ : 1.24 (3H, t, CH_3), 1.66 (3H, s, 5- CH_3), 2.32 (3H, s, 6- CH_3), 3.9–4.4 (4H, m, N- CH_2 and O- CH_2), 5.75 (1H, br, N-H), 7.43 (5H, s, Ph). MS m/e : 341 (M^+), 268. The third eluate with CHCl_3 -EtOH (30:1) gave a further 43 mg of **12**. The total yield of **12** was 0.44 g (37%). The fourth eluate with CHCl_3 -EtOH (30:1) gave 0.20 g (16%) of **14d**. Compounds **12**, **14a**, and **14d** were identical with samples obtained by the methods described above and below, respectively.

2-Amino-3-benzyl-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine Hydrochloride Hemihydrate (13b)—A mixture of 4.93 g (13 mmol) of the free base of **11b** and 1.5 ml of AcOH in 50 ml of 10% NH_3 -EtOH solution was heated at 130° for 134 hr in a sealed tube under a nitrogen atmosphere. The mixture was cooled and the precipitate was collected by filtration to recover 2.56 g (53%) of the free base of **11b**. The filtrate was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with CHCl_3 . The extract was washed with H_2O , dried and concentrated *in vacuo*. The residue was chromatographed on silica gel. The eluate with CHCl_3 -MeOH (20:1) was collected and treated with 10% HCl-MeOH solution to give 1.44 g (29%) of **13b**, mp 148–151° (from EtOH- Et_2O). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400–2700, 1640, 1540. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 240, 296; $\lambda_{\text{max}}^{\text{EtOH}-2\text{N NaOH}}$ nm: 326. NMR ($\text{DMSO}-d_6$) δ : 1.70 (3H, s, 5- CH_3), 2.19 (3H, s, 6- CH_3), 4.35, 5.12 (1H \times 2, d \times d, $J=18$ Hz, N- CH_2), 5.71 (1H, s, CH), 7.40, 7.45 (5H \times 2, s, Ph), 8.43 (3H, br s, N-H). Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_3\text{S} \cdot 0.5\text{H}_2\text{O}$: C, 64.68; H, 6.38; N, 11.01. Found: C, 64.19; H, 5.90; N, 10.69.

2-Amino-5,6-dimethyl-4-phenylthieno[2,3-d]pyrimidine (14a)—A mixture of 0.275 g (1 mmol) of **7** in 10% NH_3 -EtOH solution in a sealed tube was heated at 110° for 13 hr. After removal of the solvent, the residue was dissolved in CHCl_3 . The solution was washed with H_2O , dried and concentrated *in vacuo*. The residue was chromatographed on silica gel. The eluate with benzene gave 0.125 g of recovered **7**. The eluate with CHCl_3 gave 0.031 g (12%) of **14a**, mp 172–174° (from benzene-petr. ether). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3470, 3300, 3160, 1610, 1520. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 254, 284 (s), 345. NMR (CDCl_3) δ : 1.66 (3H, s, 5- CH_3), 2.33 (3H, s, 6- CH_3), 5.18 (2H, br s, N-H), 7.42 (5H, s, Ph). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{S}$: C, 65.86; H, 5.13; N, 16.46. Found: C, 66.13; H, 5.17; N, 16.39.

2-Benzylamino-5,6-dimethyl-4-phenylthieno[2,3-d]pyrimidine (14b)—a) A mixture of 0.275 g (1 mmol) of **7** and 0.235 g (2.2 mmol) of benzylamine in 10 ml of EtOH was heated under reflux for 92 hr. After removal of the solvent, the residue was mixed with H_2O and extracted with CHCl_3 . The extract was

washed with H₂O, dried and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with benzene to give 0.199 g (58%) of **14b**, mp 133—136° (from benzene–hexane). IR ν_{\max}^{KBr} cm⁻¹: 3260, 1580, 1550. UV $\lambda_{\max}^{\text{EtOH}}$ nm: 230 (s), 261, 289, 351. NMR (CDCl₃) δ : 1.67 (3H, s, 5-CH₃), 2.31 (3H, s, 6-CH₃), 4.67 (2H, d, N-CH₂), 4.78 (1H, br t, N-H), 7.2—7.4 (5H, m, Ph), 7.45 (5H, s, Ph). *Anal.* Calcd for C₂₁H₁₉N₃S: C, 73.01; H, 5.54; N, 12.16. Found: C, 73.02; H, 6.07; N, 12.29.

b) Chloranil (0.16 g, 0.65 mmol) was added to a solution of 0.25 g (0.72 mmol) of the free base of **13b** in 15 ml of CCl₄. The mixture was stirred at room temperature for 0.5 hr and then heated under reflux for 0.5 hr. The mixture was cooled, then diluted with CHCl₃. The solution was washed with 2 N NaOH and H₂O successively, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene to give 0.057 g (23%) of **14b**, which was identical with a specimen obtained by method a).

(5,6-Dimethyl-4-phenylthieno[2,3-*d*]pyrimidin-2-ylamino)acetamide (**14d**)—A mixture of 0.275 g (1 mmol) of **7**, 0.121 g (1.1 mmol) of glycineamide hydrochloride and 0.222 g (1 mmol) of Et₃N in 10 ml of EtOH was heated under reflux for 8 hr. After removal of the solvent, the residue was mixed with H₂O and extracted with CHCl₃. The extract was washed with H₂O, dried and concentrated *in vacuo*. The residue was triturated with benzene. The precipitate was collected and recrystallized from EtOH to give 0.035 g (11%) of **14d**, mp 215—217°. IR ν_{\max}^{KBr} cm⁻¹: 3400—2800, 1660, 1540. UV $\lambda_{\max}^{\text{EtOH}}$ nm: 229 (s), 258, 285 (s), 355. NMR (CDCl₃) δ : 1.62 (3H, s, 5-CH₃), 2.31 (3H, s, 6-CH₃), 3.86 (2H, d, *J* = 6 Hz, N-CH₂), 6.9—7.35 (3H, m, N-H), 7.46 (5H, s, Ph). *Anal.* Calcd for C₁₆H₁₆N₄OS: C, 61.52; H, 5.16; N, 17.93. Found: C, 61.01; H, 5.28; N, 17.75.

Acknowledgement The authors are grateful to Drs. Y. Abiko and S. Ashida, and Miss K. Sakuma for carrying out biological assays. Thanks are also due to the staff of this Institute for elemental analysis.